The Biology and Physiology of Aging

Discussant
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This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

FLOYD C. RECTOR, MD*: *This conference is given by Itamar Abrass, MD, Head of the Division of Gerontology and Geriatric Medicine at the University of Washington School of Medicine. Dr Abrass, who is a graduate of the University of California, San Francisco, will discuss a topic of substantial relevance to the increasing average age of the patient population: the biologic and physiologic changes of aging.*

ITAMAR B. ABRASS, MD†: The demographic imperative suggests that medical practice in the future will involve a great deal of geriatrics. Older adults presently represent more than a third of patients seen by primary care physicians; this will reach more than 50% in the next century.[1] The number of older persons (aged 65 and older) in this country has grown in both absolute and relative terms. This growth has been influenced by both an increase in the mean life span and a decrease in the birth rate. The group older than 75 years has become even larger. The result is a greater demand on the health care system.

The gain in survival includes both active and dependent years. As the mean life span has lengthened and the maximal life span has remained essentially unchanged, the concept of the compression of morbidity—that is, that the time of dependency will decrease as the life expectancy increases—has been popularized. Unfortunately, at least so far, the data do not support such an outcome. If anything, the mean prevalence of disability seems to be getting worse with time. These data appear in contrast to the clinical impression that older adults are generally healthier and more active. In fact, there may be a bimodal distribution, with some persons getting healthier and others more disabled owing to survival with an illness or disability that was previously fatal.[1] It will be important to define the factors that lead to "successful" aging. Delivering the needed health care and decreasing the time of disability present challenges to both clinicians and scientists.

With aging, two phenomena occur: There is a physiologic decline and an increase in the prevalence of disease. Although these processes influence each other, physiologic decline does occur independent of disease.

In healthy older adults, many physiologic functions are maintained in the basal resting state, but decrements are seen in most organ systems and homeostatic mechanisms when these systems are challenged or stressed. These biologic and physiologic changes of aging were recently reviewed.[2] With advanced age, acute illness is often replaced by chronic disease of multifactorial etiology. Mortality curves are exponential after age 30, with cardiovascular and neoplastic diseases being the commonest causes of death. Yet even in the most elderly persons, apart from the prevalence of disease, the interaction of disease and physiologic change remains important. Pathologists may identify many lesions without defining the cause of death. In fact, the cause of death may have been a relatively minor perturbation of homeostatic mechanisms.

The Biologic Basis of Aging

The importance of genetics in the regulation of biologic aging is shown by the characteristic longevity of each animal species. Several theories of aging have been promulgated. These theories, which have been extensively reviewed by Goldstein and co-workers,[3-5] fall into two general categories: the accumulation of damage to informational molecules, and the regulation of specific genes.

Deoxyribonucleic acid undergoes continuous change in response to both exogenous agents and intrinsic processes. Stability is maintained by the double-strandedness of DNA and by specific repair enzymes. It has been proposed that somatic mutagenesis, due to either a greater susceptibility to mutagenesis or deficits in repair mechanisms, is a factor in biologic aging. In fact, there is a positive correlation of species longevity with DNA repair enzymes. In humans, though, the spontaneous mutagenesis rate is not adequate to account for the number of changes that would be necessary to cause aging, and there is no evidence that a failure in repair systems underlies this phenomenon.

A related theory, the error-catastrophe theory, proposes that errors occur in DNA, RNA, and protein synthesis, each augmenting the others and finally culminating in an error catastrophe. Translation was considered the most likely source of age-dependent errors because it was the final common pathway. But increased translational errors have not been found during aging either in vivo or in vitro. Amino acid substitutions do not increase with aging, although some enzyme activities may be altered by changes in posttranslational modification, such as glycosylation.

The major by-products of oxidative metabolism include superoxide radicals, which can react with DNA, RNA, proteins, and lipids and lead to cellular damage and aging.

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ABBREVIATIONS USED IN TEXT

HDL = high-density lipoprotein
IL-2 = interleukin-2
LDL = low-density lipoprotein

Several scavenging enzymes and some small molecules, such as vitamin C and vitamin E, protect the cell from oxidative damage. In aging, there is no notable loss of scavenging enzymes, and vitamins C and E do not increase longevity in animals.

At present, the most favored concept of aging is that it is regulated by specific genes. Support for such a hypothesis has been gained mostly from in vitro models of aging. Adult cells can be placed into three categories based on their replicative capacity: continuously replicating, replicating in response to a challenge, and nonreplicating. For example, epidermal, gastrointestinal, and hematopoietic cells are continuously renewed; the liver can regenerate in response to injury; neurons and cardiac and skeletal muscle do not regenerate. In vitro replication is closely related to in vivo proliferation. Neurons and cardiac myocytes from adults can be maintained in culture but do not divide, whereas hepatocytes, marrow cells, endothelial cells, and fibroblasts replicate in vitro. Because they are easily obtained from skin, fibroblasts have been the most extensively studied. Although some cells continuously replicate in vivo, they have a finite replicative life.[6] For fibroblasts in vitro, this is about 50 doublings. The replicative life of fibroblasts in vitro correlates with the age of the donor: the older the donor, the fewer the doublings in vitro. With time in culture, doubling time increases and replication eventually stops.

When fibroblasts from younger donors are fused with nonreplicating senescent cells, DNA synthesis is inhibited in both nuclei. When protein synthesis is transiently inhibited immediately after fusion, DNA synthesis is increased in both nuclei, suggesting that a cytoplasmic protein factor may be involved in inhibiting replication. When senescent cytoplasts—cells without nuclei—are fused with young, dividing cells, DNA synthesis is depressed. Growth arrest both in vivo and in vitro has now been associated with the appearance of a specific protein that may be involved in DNA replication.

These experiments help us understand the finite life span of cells in vitro but do not themselves explain the process of aging in vivo, since organisms do not suddenly die because all their cells stop replicating and die. Nevertheless, factors associated with finite cell replication may have a direct influence on the aging of an organism. For example, fibroblasts aged in vitro or obtained from older adult donors are less sensitive to many growth factors. Such changes may be mediated at both the receptor and postreceptor level. A decrease in the output of growth factors, changes in cell sensitivity to growth factors, or a slowing of the cell cycle may all contribute to impaired wound healing and thus place older persons at greater risk for infection.

For tissues with nonreplicating cells, cell loss may lead to a permanent deficit. With aging, dopaminergic neurons are lost, and this loss influences gait, balance, and the susceptibility to drug side effects. With further decrements due to ischemia or viral infection, Parkinson's disease may develop. Similar cell loss, functional deficits, or both may occur in other neurotransmitter systems and lead to autonomic dysfunction and to an alteration in mental function and neuroendocrine control.

The immune system shows similar age-dependent phenomena. Lymphocytes from older adults have a diminished proliferative response to numerous mitogens. This appears to be due to both a decrease in lymphokines and a lessened response to extracellular signals. As the thymus involutes after puberty, thymic hormone (thymosin) levels decrease. Basal and stimulated interleukin-2 (IL-2) production—and IL-2 responsiveness—also diminishes with age. Diminished IL-2 responsiveness appears to be attributable, at least in part, to a decreased expression of IL-2 receptors. Some immune functions can be restored by adding these hormones or mediators to lymphocytes in vitro, or in vivo by administering them to aged animals. The proliferative defect can also be reversed in vitro by calcium inophores and activators of protein kinase C, suggesting that the T-cell defect may be in the transduction of extracellular signals to intracellular responses.

In vivo, molecular mechanisms such as those described contribute to physiologic deficits and altered homeostatic mechanisms that predispose older persons to dysfunction in the face of stress and disease.[7,8]

The Physiologic Changes of Aging

In assessing data on physiologic function with aging, several factors should be considered[9]: First, in healthy older adults, decrements in function are usually seen only under stress. Further, data generally represent means; with aging, there is usually a greater intragroup variability. Finally, most data are cross-sectional rather than longitudinal. It is also important to determine how the health status of healthy persons was defined.

Cardiovascular

An earlier study suggested that cardiac output at rest declines progressively from about age 20 to age 90.[10] The subjects in this study, however, had not been screened for occult coronary artery disease. The data are different when the population is first screened by stress thallium imaging to exclude subjects with occult coronary artery disease.[11] In this population, the resting cardiac output is unaffected by age from the third through the eighth decades. Cardiac output is also unchanged with age during graded exercise. But with aging, the heart rate decreases and end-diastolic and end-systolic volumes increase. Thus in older subjects, cardiac output during exercise is maintained by using the Frank-Starling mechanism. It seems that even healthy older persons have reserve mechanisms to maintain cardiac output and may therefore be more vulnerable to decompensation when disease is superimposed (Table 1).

These data are also consistent with the notion that myocardial β-adrenergic responsiveness decreases with age. Such changes have been shown in both humans and animals. Heart rate response to isoproterenol infusion decreases with age, and in animals, myocardial contractility decreases as well. This deficit has been shown to be specifically related to β-adrenergic mechanisms and not to intrinsic contractile abnormalities. Basal and stimulated norepinephrine levels increase with age. It is not known whether the deficit in β-adrenergic responsiveness is due to desensitization by endogenous catecholamines or to other age-related phenomena.

Diastolic dysfunction also occurs with aging, with less early diastolic filling and greater dependence on atrial contraction. Such changes may make the elderly more vulnerable to the development of congestive heart failure, particularly in patients with atrial fibrillation. Although elderly

master athletes appear to have less diastolic dysfunction than their sedentary counterparts, preliminary data showed no reversal of existing diastolic dysfunction in elderly subjects who enrolled in an exercise program.

Older persons also show decreased baroreceptor reflex sensitivity—that is, cardiovascular responses to changes in intravascular volume are altered. Such changes may put older patients at a greater risk for inappropriate volume expansion and may also contribute to the higher prevalence of orthostatic hypotension in older adults.

Pulmonary

Except for residual volume, which increases, most pulmonary volumes are unaltered in healthy nonsmoking older adults (Table 2).[12] Compliance increases, however, as the elasticity of structures decreases. The number of supporting structures for small airways also decreases. These changes in small airways lead to an increase in closing volumes such that by the mean age of 65 years, not all the airways are opened during regular breathing in a sitting position.[13] In recumbency, these airway changes occur at age 45. Thus, atelectasis and potentially a complicating pneumonia are more likely to develop in older patients—particularly when lying in bed for prolonged periods—than in younger persons.

Endocrine

The aging process is associated with the development of glucose intolerance (Table 3).[14] The primary defect seems to be one of insulin resistance; most studies show increased insulin levels. Dysregulation of insulin secretion may also be a factor in that the insulin levels may not be appropriate for the level of hyperglycemia. The cause of this impaired carbohydrate metabolism has not been fully determined. Although obesity, activity, and dietary composition influence carbohydrate metabolism, they are not the sole factors in the derangement associated with aging. At the tissue level, the insulin resistance of aging appears to be a postreceptor defect. Insulin receptor number and affinity, as measured on monocytes and adipose tissue, are unaltered with age.[15,16] The postreceptor site that is affected by age is not yet known.

Although the glucose intolerance of aging is not, strictly speaking, diabetes mellitus, it may nevertheless have important health consequences. In healthy older adults, fasting blood glucose levels remain in the normal range, but glycosylated hemoglobin levels rise.[17] Similar changes may occur in other structural proteins and enzymes to an extent that may modify their function. Insulin therapy has been shown to be an independent risk factor for atherosclerosis, and hyperinsulinemia may be a contributory factor to the prevalence of vascular disease in older adults. Even within the normal range of an oral glucose tolerance test, those having blood glucose levels at the upper range have an increased risk of coronary artery disease when compared with those with low-normal levels.

The metabolic clearance rate of thyroid hormone decreases with age.[18] With an intact hypothalamic-pituitary-thyroid axis, thyroxine levels are maintained in the normal range. Yet, with thyroid disease, when exogenous thyroxine is administered, the replacement dose must be adjusted downward to account for the change in clearance.

The most pronounced endocrine change occurs with decreased estrogen production in women during menopause. Along with the changes in reproductive tissues, there is a notable alteration in bone metabolism and, in those with other risk factors, the development of osteoporosis.

An interesting point of debate in the field of aging is the hypothesis that the sex difference in longevity is mediated by the sex difference in atherogenesis, which in turn is mediated by the sex difference in lipoprotein metabolism, and that this, in turn, is determined by gender-specific sex hormone levels.[19] During adolescence, low-density lipoprotein (LDL) levels rise and high-density lipoprotein (HDL) levels decline more in boys than in girls. At menopause, LDL levels rise in women, exceeding those in men throughout the postmenopausal period. If the LDL:HDL ratio is used as the index of atherogenic risk, the sex difference in this ratio can account for a substantial proportion of the sex difference in atherosclerosis and, thus, for a major part of the sex difference in human longevity. The high male-to-female ratio of coronary artery disease mortality progressively decreases after menopause. Although not all studies agree in their findings, several have shown a reduction in coronary artery disease incidence and in all-cause mortality in women using postmenopausal estrogens. These benefits may be mediated by the effects of estrogens on lipoprotein metabolism. Although suggestive, these studies do not directly confirm the hypothesis that relates the influence of endogenous steroids to the sex difference in longevity.

Sex hormone levels do not sharply decline in men as they do during menopause in women, but most studies have

TABLE 1.—*Characteristics of Cardiac Function in Aging*

Cardiac output during exercise achieved by
Lower heart rate
Higher end-diastolic volume
Higher stroke volume
Reliance on Frank-Starling mechanism
Decreased cardiovascular catecholamine responsiveness
Diastolic dysfunction
Diminished myocardial contractile reserve
Risk for functional compromise

TABLE 2.—*Pulmonary Function in Aging*

Increase in residual volume
Decreased elasticity of structures
Increased compliance
Decreased number of airway-supporting structures
Increase in closing volumes
Increased risk for atelectasis

TABLE 3.—*Carbohydrate Metabolism in Aging*

Glucose intolerance is common
Primary defect is insulin resistance
Dysregulation of insulin secretion
Insulin receptor number and affinity unaltered
Postreceptor defect present
Possible increased risk for vascular disease

TABLE 4.—*Fluid and Electrolyte Homeostasis in Aging*

Response to sodium restriction blunted
Less able to excrete solute load
Increased risk for hyperkalemia
Water conservation and urine concentration ability impaired
Increased osmoreceptor sensitivity and propensity for inappropriate antidiuretic secretion syndrome

shown a progressive fall in testosterone levels with aging. In most men the levels do not decrease into the hypogonadal range. Although sexual activity declines with age, this does not seem directly related to testosterone levels. We are not sure yet what effects diminishing testosterone levels have on other metabolic variables. Muscle mass and strength decline with age. How testosterone may contribute to this change has not been assessed. Future studies will need to address this issue as well as the influence of androgens on the hematopoietic system, lipoprotein metabolism, and the general well-being of older men.

Fluid and Electrolytes

Under normal circumstances there are no changes in serum sodium, potassium, hydrogen ion concentration, or vascular volume with age (Table 4). Adaptive mechanisms are nonetheless impaired, and acute illness is often complicated by derangements in fluid and electrolytes balance. The response to sodium restriction is blunted. Older adults can reach sodium balance with restriction, but the response is sluggish, and before balance is achieved, the sodium deficit is greater than in younger persons. Several factors contribute to this salt-losing tendency: With aging, there is nephron loss and a consequent increased osmotic load per nephron. Renin levels are decreased both in the basal and stimulated state. As a result of the changes in renin, aldosterone levels are decreased.

With or without preexisting myocardial disease, older adults are at increased risk for volume expansion. They are less able to excrete an elevated salt load, requiring a longer time to reestablish balance. These changes relate to a decrease in glomerular filtration rate and decreased baroreceptor reflex sensitivity. Potassium handling is also altered with age, and older adults are at increased risk for hyperkalemia. With both the glomerular filtration rate and aldosterone levels decreased, renal potassium excretion is altered. Insulin and catecholamines modulate potassium transport into cells. With decreased insulin and β-adrenergic responsiveness, these adaptive mechanisms are also diminished.

Dehydration is a problem in the elderly especially when fluid intake is limited and insensible loss is increased. Water conservation and urine-concentrating abilities are impaired with aging. Thirst mechanisms are also blunted, compromising the adaptive response to dehydration. These changes, combined with the salt-losing tendency of older persons, help explain why hypertonic volume depletion is such a common presentation.

Possibly the most serious and least well-recognized problem resulting from fluid and electrolyte imbalance in older adults is water intoxication. Again, changes in physiologic variables contribute to this disorder. Basal vasopressin levels are unaltered during normal aging, but infusing a hypertonic saline solution leads to an increase in plasma vasopressin levels that is greater than in younger persons.[20] Conversely, infusing an alcohol solution leads to a diminished suppression of vasopressin in elderly persons.[21] These data suggest increased osmoreceptor sensitivity in older adults with a higher "set point" for vasopressin secretion. Thus certain drugs and pulmonary and central nervous system disorders are more likely to precipitate the syndrome of inappropriate antidiuretic hormone secretion in older patients.

Renal

In cross-sectional studies, renal blood flow, glomerular filtration rate, and creatinine clearance levels have been shown to decrease with age. Creatinine production also diminishes, so that the serum creatinine level may not directly reflect creatinine clearance. It is important to recognize these changes and to make appropriate adjustments in the doses of drugs that are excreted primarily by the kidneys.[22] More recent longitudinal data suggest that renal function does not deteriorate in everyone with aging; in some it remains relatively unchanged, in others it deteriorates only slightly, and in still others there is a more substantial decline.[23] These differences only confirm the variability of aging; nevertheless, the decrease in renal function still must be considered, particularly in those who come under the care of a physician.

Vision and Hearing

Although easily overlooked, age-associated physiologic and functional changes in vision and hearing may contribute to significant dysfunction in older adults. Visual acuity may decrease because of changes in the retina or neural elements. Changes in refractive power lead to both increased hyperopia and myopia. A loss of accommodation leads to hyperopia, and nuclear sclerosis leads to increased lenticular refractive power and myopia. Diminished tear secretion in many older persons, especially postmenopausal women, may lead to dryness of the eyes, which can cause irritation and discomfort. This condition may endanger the integrity of the corneal surface.

Hearing changes do not occur only in the peripheral auditory system.[24] A loss of hearing of pure tones, particularly in higher frequencies—more pronounced in men—can interfere with both hearing and understanding speech. Brain-stem changes may lead to difficulty hearing and localizing sounds in noisy environments. Cortical changes may lead to problems with difficult speech and language. Thus, the changes in hearing function are much more complex than just pure tone loss.

Conclusion

With changes in the environment, mean life span has increased and is approaching that predicted by "ideal" survival curves. Maximal life span, about 120 years for humans, appears not to be changing. Newer cell biology and molecular biology techniques will almost certainly define the genetic factors that determine maximal life span. Prospects for prolonging maximal life span are currently unrealistic, though.

The molecular changes that seem to determine species longevity are most likely also associated with determinants of cellular function. In vivo, these molecular and cellular changes lead to less effective homeostatic mechanisms, increasing an organism's vulnerability to its environment. Understanding these molecular and cellular changes and the environmental influences on them should lead to interventions that increase the mean life span and, more important, decrease disability.

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RURAL ROUTE

The box beside the orange road
Waits for letters no one sends,
Through winter summer winter
Some fifteen odd or so
Passing themselves away
One into the other
Counted only by the date adding itself
To the last X on the calendar
That times the tiny pill or
Red elixir pumping life
Into a wasting frame.

On days the postman brakes, and reaches
Opening the flop-down door,
An old man picks his footing along
The rutted path, pulls forth
A catalog, a water bill or
Some group's plea
To care for starving children.
The old man turns and
Drags his feet
Back up the rutted path.
What can he tell the woman
Behind the window, waiting.

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